

# Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients with Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial

## BACKGROUND

- Hypoglycemia and concerns regarding hypoglycemia are acknowledged as the main limiting factors for achieving tight glycemic control.
- A meta-analysis of previous 5 open label trials showed that at similar HbA1c levels and lower rates of hypoglycemia among patients who received insulin degludec than among those who received insulin glargine (17% vs 32% respectively).

## OBJECTIVE

- To test whether treatment with basal insulin degludec is associated with a lower rate of hypoglycemia compared with insulin glargine U100 patients with type 2 diabetes.

## METHODS

- **Design:** Randomized, double-blind, 2-period crossover, multicenter, treat-to-target trial
- **Inclusion Criteria:** Aged 18 years old or older, diagnosed with T2D for at least 26 weeks, HbA1c level of 9.5% or lower, body mass index of 45 or lower, and treatment with any basal insulin with or without oral antidiabetics for at least 26 weeks
  - Patients had to have at least 1 of the following Hypoglycemia risk factor
    - Experienced at least 1 severe hypoglycemic episode within the last year
    - Moderate chronic renal failure
    - Hypoglycemic symptom unawareness
    - Exposure to insulin for longer than 5 years
    - Episode of hypoglycemia within the last 12 weeks
- **Exclusion criteria:** Patients with recurrent severe hypoglycemia AND patients treated with bolus or premixed insulin or with sulfonylurea or meglitinide within 26 weeks before the first visit
- **Primary outcome measure:** Rate of overall symptomatic hypoglycemic episodes during the maintenance period
- **Secondary outcome measure:** rate of nocturnal symptomatic hypoglycemic episode and the proportion of patients experiencing 1 or more severe hypoglycemic episodes in the maintenance period
- 721 patients received treatment sequence
  - 361 patients received insulin degludec followed by insulin glargine U100
  - 360 patients received insulin glargine U100 followed by insulin degludec
- Power 88.9% with an alpha level of 0.025 to demonstrate a 38% benefit with an expected rate of overall symptomatic hypoglycemia of 0.5 episodes per patient-year of exposure (PYE)
- Data handling method was intention-to-treat

## RESULTS

- Among 721 patients, 580 patients completed the study
- **Primary outcome measure:** The rate of overall symptomatic hypoglycemia during the maintenance period was statistically significantly lower with insulin degludec compared with insulin glargine U100 (185.6 vs. 265.4 episodes/100 PYE, respectively; ERR = 0.70, 95% CI, 0.61 to 0.80;  $p < 0.001$ )
- **Secondary outcome measure:**
  - The rate of nocturnal symptomatic hypoglycemia was also statistically significantly lower with insulin degludec compared with insulin glargine U100 during the

maintenance period (55.2 vs. 93.6 episodes/100 PYE, respectively; ERR = 0.58, 95% CI, 0.46 to 0.74;  $p < 0.001$ )

- The proportion of patients experiencing at least 1 severe hypoglycemia episode during the maintenance period was 1.6% (95% CI, 0.6% to 2.7%) for insulin degludec and 2.4% (95% CI, 1.1% to 3.7%) for insulin glargine U100 (difference, -0.8%, [95% CI, -2.2% to 0.5%]), but this difference was not statistically significant ( $P = 0.35$ ).
- **Author's conclusion:** Among patients with type 2 diabetes treated with insulin and with at least 1 hypoglycemia risk factor, 32 weeks' treatment with insulin degludec compared with insulin glargine U100 resulted in a reduced rate of overall symptomatic hypoglycemia

#### STRENGTHS

- Random assignment for which group get which insulin first followed by another insulin
- Double-blind
- Washout and titration period on hypoglycemic episodes

#### LIMITATIONS

- Crossover study
  - Longer duration of therapy
  - Results did not differentiate sequencing effects
  - Potential carryover effects
- Higher than expected withdrawal rate
- Potential conflicts of interest
  - Most authors are affiliated with research centers
  - Authors received research support from Novo Nordisk that supported study funding and also manufactured insulin degludec.
- Used 100 PYE rather than actual rates to show statistically significant differences

#### CONCLUSION

- Although the study showed the reduced rate of overall symptomatic hypoglycemia for insulin degludec compared with insulin glargine U100, it may not be clinically different.
  - The study used 100 PYE to show larger numbers of hypoglycemia episodes than actual incidence of hypoglycemia episodes.
  - Actual rate of hypoglycemia episode during the maintenance period was not statistically significant (1.6% for insulin degludec, 2.4% for insulin glargine).
  - Insulin degludec and insulin glargine had the similar HbA1c level reduction with the similar side effects.
- Future research
  - Since the study used crossover study design, a trial should be use more complex statistical analyses to determine possibility of carry-over or sequencing effects. OR a trial should use parallel study design to eliminate the carry-over and sequencing effects

#### REFERENCE

Wysham C, Bhargava A, Chaykin L, Rosa R, Handelsman Y, et al. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients with Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial. JAMA. 2017;318(1):45-56.